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CLINICAL ARTICLE

Cost-effectiveness of two interventions for the prevention of postpartum hemorrhage in Senegal

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ABSTRACT

Objective: To compare, at the community level, the cost-effectiveness of oxytocin and misoprostol for the prevention of postpartum hemorrhage (PPH). *Methods:* The present cost-effectiveness study used data collected during a randomized trial that compared the prophylactic effectiveness of misoprostol and oxytocin for the prevention of PPH in a rural setting in Senegal between June 6 and September 21 2013. The two interventions were compared, with referral to a higher level facility owing to PPH being the outcome measure. The costs and effects were calculated for two hypothetical cohorts of patients delivering during a 1-year period, with each cohort receiving one intervention. A comparison with a third hypothetical cohort receiving the current standard of care was included. A sensitivity analysis was performed to estimate the impact of variations in model assumptions. *Results:* The cost per PPH referral averted was US$ 38.96 for misoprostol and US$ 119.15 for oxytocin. In all the scenarios modeled the misoprostol intervention dominated, except in the worst-case scenario, where the oxytocin intervention demonstrated slightly better cost-effectiveness. *Conclusion:* The use of misoprostol for PPH prophylaxis could be cost effective and improve maternal outcomes in low-income settings.

1. Introduction

Postpartum hemorrhage (PPH) is a major cause of maternal mortality. WHO estimates that 27% of all maternal mortality is due to PPH [1]. The incidence of maternal mortality is concentrated overwhelmingly in low- and middle-income countries—WHO estimates that, out of 289 000 maternal deaths that occurred worldwide in 2013, 286 000 were in low- and middle-income countries. In this respect, the maternal mortality ratio in Senegal (320 deaths per 100 000 live births) is fairly typical of Sub-Saharan Africa [2]. Tragically, while PPH is a manageable condition in high-income countries, it can be life-threatening and often fatal in countries similar to Senegal, where access to adequate obstetric care and blood transfusions are limited.

Prophylactic administration of either misoprostol or oxytocin immediately after delivery has been shown to be effective in preventing PPH [3,4]. Both have been recommended by WHO for the prevention and treatment of PPH, although oxytocin remains the drug of choice [5–8]. However, oxytocin requires cold-chain logistics because it degrades at room temperatures or higher; additionally, it must be administered parenterally. These requirements make oxytocin more difficult to use in situations where trained practitioners and medical infrastructure are relatively scarce. Conversely, misoprostol is thermostable and available in tablet form, making transportation, storage, and administration easy.

Whereas several clinical studies have demonstrated superior efficacy for oxytocin compared with misoprostol in the prevention of PPH [9], to the best of our knowledge no studies have examined the relative merits of these two drugs in a community-level setting, under sub-optimal conditions where many deliveries take place (i.e. either at patients' home or at sub-centers with only traditional birth attendants to assist during deliveries) [10–13]. The aim of the present cost-effectiveness analysis was to compare the use of oxytocin and misoprostol for the prevention of PPH in a community-based setting.

2. Materials and methods

The present cost-effectiveness analysis used data from a cluster randomized trial conducted at the community level in three predominantly rural districts of Senegal between June 6 and September 21, 2013 that compared the effectiveness of misoprostol (600 μg administered orally) and oxytocin (10 IU administered intramuscularly via the Uniject system [Instituto Biologico Argentina S.A.I.C., Buenos Aires, Argentina]) for the prevention of PPH during the third stage of labor [14]. The present cost-effectiveness analysis was approved by the National

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Council on Health Research, National Ethical Committee, Ministry of Health and Prevention, Senegal as part of the cluster randomized trial [14]. No specific patient data was used in the present analysis so it was not necessary to obtain informed consent.

The study protocol for the randomized trial has been described in detail elsewhere [14] and will only be summarized briefly here. The study was conducted by auxiliary midwives (matrones) at 28 village "health huts" (maternity huts with a delivery table but no instruments or medications), with 14 huts included in each treatment arm. All patients attending the health huts for delivery who consented were included in the trial. The primary outcome measure was the change in hemoglobin level, measured at a prenatal visit before delivery and again within 48 h of delivery. Referral to health centers or hospitals for treatment for PPH was recorded in the study as a secondary outcome measure, as were drops in hemoglobin of 20 g/L or more.

There was no significant difference in the change in hemoglobin level between the two study arms. No significant difference was observed in the mean decrease in hemoglobin count pre- and post-intervention between the two arms. The referral rates owing to PPH were 0.0% (95% confidence interval 0.0–1.2) in the misoprostol arm and 0.2% (95% confidence interval 0.0–2.0) in the oxytocin arm. There were no PPH-attributed deaths in the trial and no serious adverse events occurred in either arm, although shivering was more common in the misoprostol arm [14].

Utilizing the data and findings from the randomized trial, the present cost-effectiveness analysis was conducted to compare misoprostol and oxytocin (administering via Uniject) for the prevention of PPH at the community level. The primary outcome was referral to a health center or hospital for PPH. This measure was a proxy variable for PPH because the main study did not measure PPH directly (i.e. postpartum blood loss ≥500 mL).

Costs and effects were calculated for two hypothetical cohorts, each consisting of 150 000 patients delivering during a 1-year period. Each cohort was assumed to have received either misoprostol or oxytocin. This number was chosen to approximate the annual number of non-institutional births that presently occur in Senegal [15,16]. A third cohort of the same size was assumed to use the current standard of care practices.

Costs were calculated in 2013 US dollars. A health-system perspective was adopted so costs incurred by the patient, their family, or society, including losses in productivity and income, or other social, psychological, and intergenerational costs were not included.

For each intervention, the total cost per delivery was calculated as the sum of the commodity cost (misoprostol or oxytocin), the cost of training matrones to administer the drug, distribution and administration costs, cold-chain costs, and wastage costs (Table 1). The commodity cost of oxytocin per delivery (US$ 1.44) was derived directly from invoices collected during the randomized trial [14] and included shipping and insurance fees, as well as a handling fee for refrigeration. The commodity cost for misoprostol (US$ 0.42) was obtained from local organizations based on the costs of recent purchases.

Table 1
Prophylactic PPH intervention costs, Senegal, 2013.[a]

Cost component	Intervention	
	Misoprostol	Oxytocin
Matrone training	1.68	1.86
Commodity	0.42	1.44
Wastage	0.02	0.17
Cold-chain logistics	NA	0.84
Distribution/use	0.09	0.06
Total	2.21	4.38

Abbreviations: PPH, postpartum hemorrhage; NA, not applicable.
[a] Intervention costs are given in 2013 US dollars.

The time taken to train matrones to be able to competently administer the study drugs was used to calculate the training cost. The per-delivery training costs were US$ 1.86 for oxytocin and US$ 1.68 for misoprostol.

It was estimated that the cost of distributing and using the two drugs contributed little to the total cost per delivery; these costs were US$ 0.06 for oxytocin and US$ 0.09 for misoprostol. The computations required various assumptions but the measurement errors that these assumptions could have introduced to the overall cost calculation were slight (computational details in Supplementary material S1).

The cost of wastage in the logistics of supplying the two drugs was also calculated. It was not possible to find an estimate of wastage for misoprostol tablets in the public drug supply system. The wastage rate for misoprostol in the randomized trial was less than 1% [14]. However, this rate was from a controlled study and so could be unrepresentative of typical wastage rates; consequently, a commonly used wastage rate of 5% was included. For oxytocin, the wastage rate from the randomized study [14] was used; of the Uniject devices, 12.1% were discarded owing to breakage, being compromised by heat, or having passed the expiration date. Consequently, the estimated cost of wastage per delivery was US$ 0.17 for oxytocin and US$ 0.02 for misoprostol.

Finally, a per-delivery cost of maintaining a cold chain for oxytocin was estimated; this estimate considered that the cold chain only extends to the health center/rural hospital level (oxytocin in Uniject form was not kept refrigerated at the health-hut level). Data regarding annual outlays for existing cold-chain logistics were obtained from the ministry of health (computational details in Supplementary material S1). The cold-chain component was estimated to add US$ 0.84 to the total per-delivery cost of oxytocin.

The two outcomes recorded in the randomized trial that were available for the present cost-effectiveness analysis were decreases in hemoglobin of at least 20 g/L and patients referred to health centers or hospitals owing to PPH. The methodological challenges in measuring PPH have been widely acknowledged [17], and the relationship between hemoglobin decreases and blood loss are not well established; some studies have reported a positive correlation and others have found none [18–22]. In view of this uncertainty, this measure of effectiveness was not included in the present analysis, which used the rate of PPH referrals.

The effects of the two prophylactic interventions were compared to the current standard of care in rural Senegal. In such areas, individuals often undergo delivery at home or in a health hut with no equipment or drugs to provide basic emergency obstetric care and no trained professional to deliver such care; consequently, the standard of care in these areas is the referral of patients to a higher-level facility for PPH. It was assumed that the rate of PPH referrals under standard of care would be equivalent to the incidence of severe PPH (blood loss >1000 mL); this was based on the assumption that all referrals reached higher-level facilities. A published estimate of 3% of deliveries among rural populations was used [23]; consequently, under standard of care, a PPH-referral rate of 3% was assumed.

Incremental costs were calculated as the difference between the cost of providing misoprostol or oxytocin to a cohort of 150 000 patients undergoing delivery versus the cost associated with applying the standard of care to the same cohort. The incremental outcomes were the difference between the number of PPH referrals in the two intervention arms and the same outcome under the standard of care. Incremental costs and incremental outcomes were used to calculate incremental cost-effectiveness ratios (ICERs). ICERs represent the incremental change in costs of an intervention divided by the incremental change in outcome following the intervention. Statistical significance (or lack of significance) in the randomized study was assumed to carry over to the cost-effectiveness analysis.

A univariate sensitivity analysis was performed to examine how uncertainty in several of the parameters that fed into ICER calculations could affected the study findings, and to determine which variables

had the largest effect on ICERs when their values were altered. The 95% confidence intervals reported in the randomized study were used to determine the upper and lower limits for these variables. For other parameters, increases and decreases of 25% from the central estimates were used. The maximum and minimum values of the variables are summarized in Table 2.

3. Results

Under baseline conditions—using central estimates for all parameters—a cohort of 150 000 patients undergoing delivery would experience 74 referrals for severe PPH when using prophylactic misoprostol, compared with 490 referrals among a cohort of patients treated with prophylactic oxytocin. In comparison with the standard of care, using misoprostol would avert 4666 PPH referrals, while using oxytocin treatment reduced the number of referrals for PPH by 4250 (Table 3). The corresponding ICERs were US$ 38.96 per PPH case averted using misoprostol and US$ 119.15 per PPH case averted using oxytocin. Consequently, the misoprostol intervention was demonstrated to dominate the oxytocin arm.

Best-case and worst-case scenarios, using the misoprostol arm of the study as the reference point, were also calculated. In the best-case scenario, all variables were assigned their lowest or highest values (Table 2), depending on which would result in a lower ICER in the misoprostol arm. In the worst-case scenario, variables were assigned in the opposite pattern, to produce the least-favorable ICER in the misoprostol arm (and the most-favorable ICER in the oxytocin arm). The misoprostol arm dominated the oxytocin arm in both the baseline and best-case scenarios (Table 3). In worst-case conditions, the oxytocin arm was slightly more cost effective than the misoprostol arm. Consequently, the prevention of PPH referrals using misoprostol dominated prophylactic oxytocin (in Uniject format), except under the unlikely assumption that all the underlying variables held values that were extremely unfavorable to misoprostol treatment.

A sensitivity analysis was performed by replacing, in turn, the baseline value of each variable with its lowest value and then with its highest value (Table 2). The results of the sensitivity analysis were plotted using a tornado diagram (Fig. 1). This analysis determined cost-effectiveness by comparing the ICERs of the two arms of the study–the sensitivity of the ratio between the oxytocin ICER and the misoprostol ICER to changes in variable values was examined. In the baseline scenario, this ratio was 3.1 (119.15/38.96), meaning that the oxytocin ICER was 3.1-times greater than the misoprostol ICER. The size of the bar for a parameter is used to illustrate how sensitive the relative cost-effectiveness is to changes in the value of that parameter, with larger bars demonstrating that the relative cost-effectiveness is very sensitive to changes in a variable.

The relative cost-effectiveness of misoprostol in comparison with oxytocin was most sensitive to changes in the rate of PPH referrals following oxytocin treatment. By way of example, if the PPH-referral rate of patients treated with oxytocin was increased to the upper limit of the confidence interval, the cost of preventing one PPH referral using oxytocin would be 8.7-times greater than the cost of preventing one PPH referral using misoprostol. Changes in the cost of misoprostol also affected its relative cost-effectiveness, though to a lesser extent than the PPH-referral rate following treatment with oxytocin. Moderate sensitivity to changes in the cost of oxytocin, changes in the PPH-referral rate after misoprostol treatment, and the cost of standard of care were also demonstrated. The proportion of patients receiving treatment with misoprostol or oxytocin had a minimal effect on the relative cost-effectiveness of the two interventions. The results of the sensitivity analysis demonstrated that treatment with misoprostol dominated oxytocin regardless of the changes made to the relevant variables.

Table 2
Baseline, maximum, and minimum values of variables included in ICER calculations.

Variable	Baseline	Minimum	Maximum
Costs of misoprostol intervention, 2013 US$			
Matrone training[b]	1.68	1.35	2.1
Commodity[a]	0.42	0.34	0.53
Wastage[a]	0.02	0.02	0.03
Cold-chain logistics[b]	NA	NA	NA
Distribution/use[b]	0.09	0.07	0.11
Costs of oxytocin intervention, 2013 US$			
Matrone training[b]	1.86	1.49	2.33
Commodity[a]	1.44	1.15	1.80
Wastage [b]	0.17	0.14	0.22
Cold-chain logistics[b]	0.84	0.67	1.05
Distribution/use[b]	0.06	0.05	0.08
Cost of standard of care, 2013 US$ [c]			
Minimal inputs	1.00	0.80	1.25
Outcomes under misoprostol[d]			
Patients referred to health centers of hospitals owing to PPH, %[e]	0	0	1.2
Outcomes under oxytocin[d]			
Patients referred to health centers of hospitals owing to PPH, %[e]	0.2	0	2.0
Other outcomes			
Patients experiencing severe PPH during delivery, %[f]	3.2	2.5	4.0
Patients receiving misoprostol during delivery, %[e]	98.4	98.2	98.7
Patients receiving oxytocin during delivery, %[e]	95.8	95.4	96.1

Abbreviations: ICER, incremental cost-effectiveness ratio; NA, not applicable; PPH, postpartum hemorrhage.

[a] Baseline data from [14]; minimum and maximum values are ±25% of the baseline value.

[b] Baseline data from unpublished reports and data from the government of Senegal; minimum and maximum values are ±25% of the baseline value.

[c] Cost of US$ 1 was assumed for the standard of care (including matrones time and incidental medicines such as analgesics).

[d] The difference in patient outcomes between the misoprostol and oxytocin interventions in [14] were not statistically significant.

[e] Baseline data from [14]; minimum and maximum values are represent 95% confidence intervals for the outcome.

[f] Baseline data from [23]; minimum and maximum values are ±25% of the baseline value.

4. Discussion

The present study demonstrated that, although the prophylactic administration of misoprostol or oxytocin immediately after delivery showed equally efficacy in reducing PPH, misoprostol was more cost effective in a rural health-hut setting. The lower cost of treatment with misoprostol in comparison with oxytocin was the primary factor driving this result. These findings are further bolstered when considering that the oxytocin intervention in the present study utilized the Uniject storage/delivery system, which obviated the need for the cold chain to reach the health-hut level and necessitated less training for matrones than traditional formulations of oxytocin (ampoules, syringes, etc.). Without the Uniject system, the logistics of using oxytocin would have been substantially more expensive because it would have been necessary for the cold chain to extend to the health-hut level [24]. The findings of the present study are highly relevant in Senegal, where maternal mortality is a major health problem and a significant proportion of pregnancy deliveries take place in patients' homes or at rural health huts; consequently, finding cost-effective interventions that help prevent PPH is a health-policy priority.

A limitation of the present study is that, although matrones were trained to recognize the signs of incipient PPH, some subjectivity remained in making patient-referral decisions. Another source of uncertainty was the incidence of PPH in the absence of an adequate standard of health care. It was necessary to rely on findings in the literature to estimate the incidence of severe PPH. However, the sensitivity analysis demonstrated that changes in the incidence of severe PPH would have

Table 3
Cost-effectiveness of prophylactic misoprostol and oxytocin to prevent referral to health centers of hospitals owing to PPH when applied to 150 000 patients undergoing delivery.

Cost scenario	No. expected referrals	No. referrals averted	Treatment costs for 150 000 deliveries, 2013 US$	Increase in costs compared with the standard of care, 2013 US$	ICER
Baseline					
Misoprostol	74	4666	331 758	181 758	38.96
Oxytocin	490	4250	656 388	506 388	119.15
Standard of care	4740	0	150 000	NA	NA
Worst-case scenario (favoring oxytocin)					
Misoprostol	1827	2913	414 697	264 697	90.86
Oxytocin	186	4554	525 110	375 110	82.37
Standard of care	4740	0	150 000	NA	NA
Best-case scenario (favoring misoprostol)					
Misoprostol	86	4654	265 406	115 406	24.80
Oxytocin	3129	1611	820 485	670 485	416.29
Standard of care	4740	0	150 000	NA	NA

Abbreviations: PPH, postpartum hemorrhage; ICER, incremental cost-effectiveness ratio; NA, not applicable.

exerted only a small effect on the study outcome (standard of care referral rate in Fig. 1).

A full scale-up of PPH prevention using misoprostol would cost the Senegal health system approximately US$ 332 000 annually (assuming that the intervention covered all deliveries taking place at patients' homes or in health huts) and would avert 4666 referrals for severe PPH. General estimates can be made for the effects of such a scale-up on maternal mortality in Senegal. Currently, approximately 1740 maternal deaths occur each year in Senegal and, of these, perhaps 720 are patients undergoing delivery at health huts. Here it has been assumed that patients undergoing delivery at health huts would have a higher maternal mortality ratio than the general population. For this illustrative example, the maternal mortality ratio was estimated to be 50% higher than the national average (320 per 100 000 live births). [2] Using WHO estimates that 27% of maternal deaths are due to PPH, approximately 195 deaths could be attributed to complications of PPH among patients undergoing delivery in health huts. If it is further assumed that the "natural" incidence rate of severe PPH is approximately 3% among deliveries, then the reduction in need for PPH referrals arising from this preventive intervention would translate to approximately 192 fewer maternal deaths annually. It is unlikely that any single intervention would almost entirely eliminate one component of maternal mortality; however, the results of the randomized trial did demonstrate zero referrals for PPH in the misoprostol treatment arm. The estimated ICER for averting one maternal death due to PPH using misoprostol would be approximately US$ 1700. This cost is comparable to WHO recommendations of interventions that are "highly cost-effective" (US$ 800) and "cost-effective" (US$ 2400) [25,26].

Clinical studies in hospital settings have demonstrated that misoprostol, administered immediately after delivery, is effective in the prevention of PPH and that its effectiveness is broadly equivalent to that of oxytocin. These studies have demonstrated the side effects of misoprostol to be mild, short lasting, and generally acceptable to patients [9]. The present study demonstrated that, in a rural community setting with only minimal healthcare provided by matrones, the prophylactic use of misoprostol was a more cost-effective strategy compared with the use of oxytocin. Furthermore, introducing this intervention nationally would reduce maternal deaths and maternal morbidity, and reduce healthcare costs associated with treating patients referred because of PPH. This would offset the cost of implementing this intervention nationwide and could result in net savings. If the average costs incurred by the health system per PPH referral were greater than the ICER (US$ 38.96), then introducing this preventive intervention would result in a net saving. These findings suggest that in countries characterized by a substantial proportion of births taking place without the presence of skilled health providers, implementation of prophylactic misoprostol-based PPH prevention would be cost effective and help improve maternal health in low- and middle-income countries.

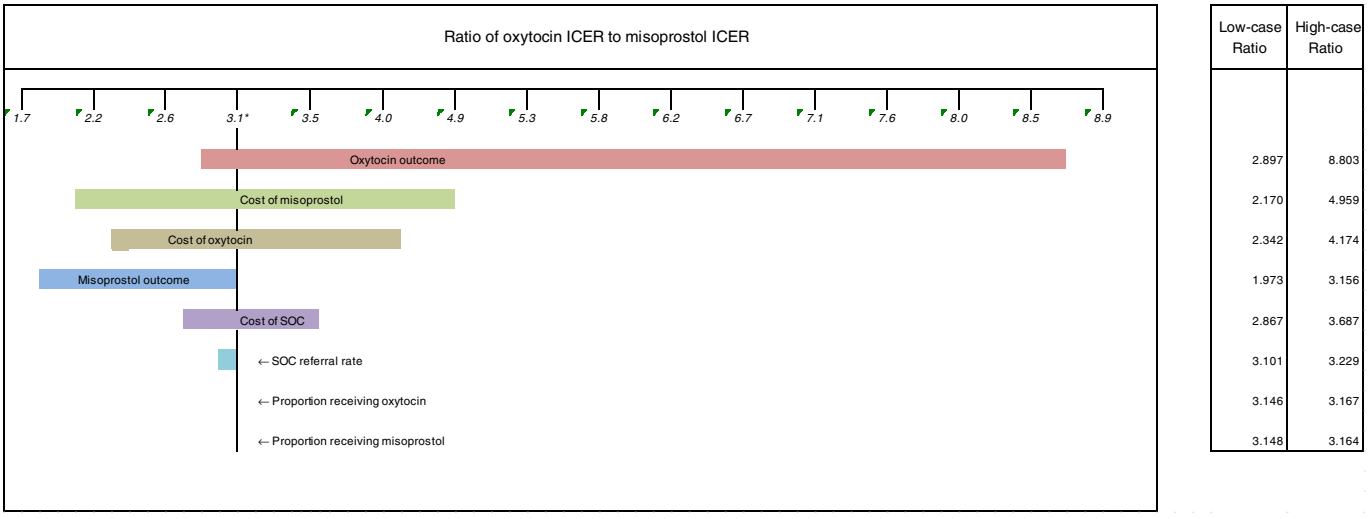

Fig. 1. Tornado diagram of ratio of oxytocin and misoprostol ICERs, with the outcome, "PPH referral". The baseline ratio between the oxytocin and misoprostol ICERs was 3.1. Abbreviation: ICER, incremental cost-effectiveness ratio.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijgo.2015.10.015.

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Conflict of interest

The authors have no conflicts of interest.

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